

Pediatric Rheumatology: Contents

Q: Approach to a Child with Joint Pain	3
Q: Diagnostic Criteria for Juvenile Idiopathic Arthritis (formerly known as Juvenile Rheumatoid Arthritis).....	6
Q: Classification and features of JRA/JIA; Write the current classification used in JRA. Tabulate differentiating features of various types of juvenile Rheumatoid arthritis.	8
Q: Tabulate the differentiating features of various types of JRA.	10
Q: Outline a scheme of investigation for a child with suspected JIA.	11
Q: Management of juvenile idiopathic arthritis (JIA/ earlier JRA); Outline the management plan for JRA.	12
Q: A) Disease modifying agents used for JIA ; B) Biological anti-TNF agents for JIA	14
Biologic therapy in JIA	16
Q: Systemic-onset Juvenile Idiopathic Arthritis (SOJIA).....	18
Q: A seven-year-old girl is admitted with pain and swelling of right knee and left ankle joint of two weeks' duration. Enumerate the likely causes. Discuss the differential diagnosis highlighting important pointers in history, examination and investigations.....	20
Q: Macrophage Activation Syndrome (MAS) (in the Context of Rheumatic Diseases).....	21
Q: SLE-Diagnostic criteria.....	23
Q: Cutaneous Manifestations of Lupus Erythematosus	25
Q: How do you classify and treat lupus nephritis	27
Q: Clinical Features of Juvenile Dermatomyositis.....	29
Q: Diagnosis and management of juvenile dermatomyositis	31
Q: Clinical Features/presentation of Kawasaki Disease	33
Q: Phases of Kawasaki Disease	36
Q: Diagnostic Criteria for Kawasaki Disease (KD).....	38
Q: Differential Diagnosis of Kawasaki Disease (KD)	40

Q: Pathogenesis of Kawasaki Disease (KD)	41
Q: Complications of Kawasaki Disease (KD).....	43
Q: Echocardiography in Kawasaki Disease (KD)	45
Q: Algorithmic approach to a suspected case of Kawasaki disease	46
Q: Treatment of Kawasaki Disease (KD).....	48
Q: Role of salicylates in Kawasaki disease	50
Q: Classification of Vasculitis Based on Size of Involved Vessels.....	51
Q: Takayasu's Arteritis ; Describe etiology, clinical features and management of Takayasu's arteritis	53
Q: Henoch-Schönlein Purpura (HSP)	54
Q: Describe the diagnostic approach and management of a six-year-old child presenting with purpuric rash and pedal edema following an episode of acute diarrhoea	56
Q: Criteria for diagnosis of Rheumatic fever	59
Q: Prophylaxis of Rheumatic fever.....	60
Q: Macrophage activation syndrome.....	61
Q: Tabulate the differences in clinical and laboratory features of Kawasaki disease and MIS-C.	64

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Q: Approach to a Child with Joint Pain

- Joint pain in children is a complex symptom with a multitude of potential etiologies, ranging from benign conditions like growing pains to serious diseases like juvenile idiopathic arthritis or malignancies.
- A systematic approach is essential for accurate diagnosis and effective management.

Clinical Evaluation

History Taking

- Onset, duration, and pattern of pain
- Associated symptoms like fever, rash, or weight loss
- Previous treatments and their outcomes
- Family history of similar symptoms or known genetic disorders

Physical Examination

- Inspection for joint swelling, redness, or deformity
- Palpation for tenderness or warmth
- Range of motion assessment
- Neurological and systemic examination

Diagnostic Tests

Laboratory Tests

- Complete Blood Count (CBC)
- Erythrocyte Sedimentation Rate (ESR)
- Rheumatoid factor, Antinuclear Antibody (ANA) for suspected autoimmune conditions

Imaging

- X-ray for structural abnormalities
- MRI for soft tissue involvement
- Ultrasound for effusion or synovitis

Differential Diagnosis

Benign Conditions

- Growing pains
- Overuse syndromes
- Musculoskeletal strain

Inflammatory Conditions

- Juvenile idiopathic arthritis
- Systemic lupus erythematosus

Infectious Causes

- Septic arthritis
- Lyme disease

Malignancies

- Leukemia
- Neuroblastoma

Management Strategies

Pharmacological

- NSAIDs for pain relief naproxen
- Disease-modifying antirheumatic drugs (DMARDs) for inflammatory conditions

Non-Pharmacological

- Physical therapy
- Occupational therapy
- Cognitive-behavioral therapy for chronic pain

Surgical

- Joint aspiration or biopsy for diagnostic clarification
- Surgical intervention for severe deformities

Table:

Diagnostic Tests	Indications
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CBC, ESR	All cases
Rheumatoid factor, ANA	Suspected autoimmune conditions
X-ray, MRI, Ultrasound	Structural or soft tissue abnormalities

Table: Differential Diagnosis of Joint Pain/JIA in Children

Differential Diagnosis	Clinical Features	Laboratory Tests	Treatment
Growing Pains	Evening leg pain, no morning symptoms, normal physical exam	Normal	Reassurance, OTC pain relief
Overuse Syndromes	Pain localized to overused joint, no systemic symptoms	Normal	Rest, NSAIDs
Musculoskeletal Strain	Localized pain, possible swelling	Normal	Rest, Ice, Compression, Elevation (RICE)
Juvenile Idiopathic Arthritis (JIA)	Joint swelling, morning stiffness, possible fever	Elevated ESR, ANA, Rheumatoid factor	NSAIDs, DMARDs, biologics
Systemic Lupus Erythematosus (SLE)	Joint pain, rash, fever, renal symptoms	Elevated ESR, ANA, dsDNA	Corticosteroids, antimalarials, immunosuppressants
Septic Arthritis	Acute onset, fever, localized redness and warmth	Elevated WBC, positive culture	Antibiotics, surgical drainage
Lyme Disease	Joint pain, erythema migrans, possible neurological symptoms	Positive Lyme serology	Antibiotics

Leukemia	Bone pain around the joint not joint per se, night cries, fatigue, pallor	Abnormal CBC, bone marrow biopsy	Chemotherapy, supportive care
Neuroblastoma	Bone pain, possible abdominal mass	Elevated catecholamines, abnormal imaging	Chemotherapy, surgical resection
Fibromyalgia	Widespread pain, fatigue, sleep disturbances	Normal	Cognitive-behavioral therapy, medications for pain and sleep
Psoriatic Arthritis	Joint pain, possible skin lesions	Elevated ESR, negative Rheumatoid factor	NSAIDs, DMARDs, biologics
Inflammatory Bowel Disease	Lower extremity joint pain, gastrointestinal symptoms	Elevated ESR, microcytic anemia	Anti-inflammatory drugs, immunosuppressants
Hypermobility	Joint pain especially in lower extremities, no systemic symptoms	Normal	Physical therapy, pain management
Orthopedic Conditions	Localized pain, possible deformity	Imaging	Depending on condition, may require surgery

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Q: Diagnostic Criteria for Juvenile Idiopathic Arthritis (formerly known as Juvenile Rheumatoid Arthritis)

Inclusion Criteria:

1. **Age of Onset:** Below 16 years of age.
2. **Duration:** Arthritis in one or more joints lasting for at least 6 weeks.
3. **Exclusion of Other Conditions:** Other conditions known to cause arthritis must be excluded.

Subtypes and Additional Criteria:

1. **Oligoarticular JIA**: Involvement of up to 4 joints during the first 6 months of disease.
 - **ANA Positive**: Increased risk of developing uveitis.
2. **Polyarticular JIA (RF Negative)**: Involvement of 5 or more joints during the first 6 months; Rheumatoid Factor (RF) negative.
3. **Polyarticular JIA (RF Positive)**: Involvement of 5 or more joints during the first 6 months; RF positive on at least two occasions at least 3 months apart.
4. **Systemic JIA**: Arthritis with or preceded by at least 2 weeks of daily fever; plus one or more of the following:
 - Evanescent (non-fixed) erythematous rash
 - Generalized lymph node enlargement
 - Hepatomegaly or splenomegaly
 - Serositis
5. **Enthesitis-Related JIA**: Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following:
 - Sacroiliac joint tenderness
 - Inflammatory lumbosacral pain
 - Presence of HLA-B27 antigen
 - Acute (symptomatic) anterior uveitis
 - History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
6. **Psoriatic JIA**: Arthritis and psoriasis, or arthritis and at least two of the following:
 - Dactylitis
 - Nail pitting or onycholysis
 - Psoriasis in a first-degree relative

Laboratory Tests:

- **Rheumatoid Factor (RF)**: For classification into RF-positive or RF-negative subtypes.

- **Anti-Nuclear Antibody (ANA):** For risk stratification, especially in oligoarticular JIA.
- **HLA-B27:** In cases of suspected enthesitis-related JIA.

Imaging:

- **X-ray:** To assess joint damage.
- **MRI:** For early detection and evaluation of joint and soft tissue involvement.

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Q: Classification and features of JRA/JIA; Write the current classification used in JRA. Tabulate differentiating features of various types of juvenile Rheumatoid arthritis.

Criteria for the Classification of Juvenile Idiopathic Arthritis:

- Age at onset: <16 yrs.
 - Duration of disease: >6 weeks
 - Arthritis swelling or effusion, or the presence of 2 or more of the following signs in >1 joint:
 - limitation of range of motion,
 - tenderness or pain on motion,
 - increased heat
 - Onset type defined by type of articular involvement in the first 6 months after onset:
 - Polyarthritis: >5 inflamed joints
 - Oligoarthritis: <4 inflamed joints
 - Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
 - Exclusion of other forms of juvenile arthritis
-
- **Epidemiology:** No sex predominance in systemic JIA, but more girls than boys are affected in both oligoarticular (3:1) and polyarticular (5:1) JIA. The peak age at onset varies for different types.
 - **Etiology:** The etiology and pathogenesis of JIA are largely unknown. It represents a heterogeneous group of disorders sharing the clinical manifestation of arthritis. Genetic factors play a role, but the genetic component is complex.

Classification and Features of Juvenile Idiopathic Arthritis (JIA)/ ILAR classification of juvenile idiopathic arthritis

Classification of JIA	Definition and Criteria	Clinical Features	Exclusions and Special Notes
Systemic JIA	Arthritis in ≥ 1 joint with fever of at least 2 weeks. Accompanied by ≥ 1 of the following: evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly or splenomegaly, serositis.	Fever, rash, lymphadenopathy, hepatosplenomegaly, serositis.	Excludes psoriasis, HLA-B27 positive arthritis after 6th birthday, ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, acute anterior uveitis, IgM RF on at least 2 occasions at least 3 months apart.
Oligoarthritis	Arthritis affecting ≤ 4 joints.	Typically affects large joints like knees; may have uveitis.	-
Polyarthritis	Arthritis affecting ≥ 5 joints.	Affects both small and large joints; may be Rheumatoid Factor positive or negative.	-
Psoriatic Arthritis	Arthritis with psoriasis or a family history of psoriasis.	Skin lesions, dactylitis, and nail pitting may be present.	-
Enthesitis-Related Arthritis (ERA)	Arthritis with enthesitis or arthritis or enthesitis with at least two other features such as sacroiliac joint tenderness, inflammatory	Lower back pain, heel pain, joint pain. May also have acute anterior uveitis.	Excludes rheumatoid factor-positive arthritis and other forms of JIA.

	lumbosacral pain, or HLA-B27 positivity.		
Undifferentiated Arthritis	Arthritis that does not fit into the other categories or fits into more than one of the above categories.	Varies; does not meet criteria for other subtypes or meets criteria for more than one subtype.	-

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Q: Tabulate the differentiating features of various types of JRA.

<i>Feature/Criteria</i>	Oligoarticular JIA	Polyarticular JIA (RF Negative)	Polyarticular JIA (RF Positive)	Systemic JIA	Enthesitis-Related JIA	Psoriatic JIA
Age of Onset	<16 years	<16 years	<16 years	<16 years	<16 years	<16 years
Number of Joints Affected	≤ 4	≥ 5	≥ 5	≥ 1	≥ 1	≥ 1
Duration	≥ 6 weeks	≥ 6 weeks	≥ 6 weeks	≥ 6 weeks	≥ 6 weeks	≥ 6 weeks
Rheumatoid Factor (RF)	Negative	Negative	Positive	Negative	Negative	Negative
ANA Status	Often Positive	Variable	Variable	Negative	Negative	Negative
Systemic Features	None	None	None	Fever, rash, etc.	None	Psoriasis
HLA-B27	Negative	Negative	Negative	Negative	Positive	Negative
Uveitis Risk	High	Low	Low	Low	Low	Low
Extra-Articular Manifestations	None	None	None	Serositis, etc.	Enthesitis	Dactylitis, etc.
Typical Age Group	Younger children	Any age	Older children/a adolescents	Any age	Older children/adolescents	Any age

Family History	None	None	None	None	Spondyloarthropathies	Psoriasis
Treatment	NSAIDs, IA steroids	DMARDs, NSAIDs	DMARDs, NSAIDs	DMARDs, Steroids	DMARDs, NSAIDs	DMARDs, NSAIDs

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Q: Outline a scheme of investigation for a child with suspected JIA.

- **Initial Screening Tests**
 - Complete Blood Count (CBC)
 - Erythrocyte Sedimentation Rate (ESR)
 - C-Reactive Protein (CRP)
- **Rheumatoid Markers**
 - Rheumatoid Factor (RF)
 - Anti-Cyclic Citrullinated Peptide (Anti-CCP)
 - Anti-Nuclear Antibody (ANA)
- **Joint Imaging**
 - X-rays of affected joints
 - Ultrasound
 - Magnetic Resonance Imaging (MRI) if needed
- **Joint Fluid Analysis**
 - Arthrocentesis for synovial fluid examination
- **HLA-B27 Testing**
 - For suspected enthesitis-related JIA
- **Biochemical Tests**
 - Liver Function Tests (LFTs)
 - Renal Function Tests (RFTs)
- **Muscle Enzyme Tests**
 - Creatine Kinase (CK)
 - Aldolase

- **Cardiac Assessment**
 - Echocardiogram for suspected systemic JIA with cardiac involvement
- **Ophthalmologic Examination**
 - Slit-lamp examination for uveitis
- **Skin Examination**
 - For psoriatic features in suspected psoriatic JIA
- **Bone Density Test**
 - Dual-energy X-ray absorptiometry (DXA) for suspected osteoporosis
- **Consultations**
 - Rheumatology
 - Ophthalmology – slit lamp exam
 - Dermatology
 - Orthopedics
- **Additional Tests**
 - Tuberculosis test (Mantoux or IGRA) if considering immunosuppressive treatment
 - Hepatitis B and C serology

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Q: Management of juvenile idiopathic arthritis (JIA/ earlier JRA); Outline the management plan for JRA.

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. The management of JIA is multifaceted and aims to reduce inflammation, control pain, maintain function, and prevent joint damage.

- **Goals of Management:**
 - Achieve disease remission or control with minimal side effects.
 - Optimize physical and psychosocial growth and development.
 - Minimize joint damage and functional disability.

- **Non-pharmacological Interventions:**

- **Physical and Occupational Therapy:** Essential for maintaining joint mobility, muscle strength, and preventing deformities.
- **Joint Protection:** Techniques and devices to protect joints from damage.
- **Patient and Family Education:** Crucial for understanding the disease, treatment options, and coping mechanisms.

- **Pharmacological Interventions:**

1. Non-steroidal Anti-inflammatory Drugs (NSAIDs):

- Examples: Naproxen, Ibuprofen.
- Primarily used to control pain and inflammation.

2. Disease-Modifying Anti-Rheumatic Drugs (DMARDs):

A. Non-biological DMARDs:

Methotrexate: Often the first-choice DMARD for JIA. Helps in reducing joint inflammation.

Sulfasalazine: Especially beneficial for children with enthesitis-related arthritis.

Leflunomide: An alternative for children who can't tolerate methotrexate.

Hydroxychloroquine: Sometimes used, especially in oligoarticular JIA.

Cyclosporine and Azathioprine: Mainly used for systemic JIA.

Cyclophosphamide and Mycophenolate Mofetil: Used in more severe cases or when other treatments fail.

B. Biological DMARDs:

TNF-alpha Inhibitors: Such as etanercept, adalimumab. Effective for treating various subtypes of JIA.

Interleukin (IL) Blockers: Including tocilizumab (IL-6 receptor blocker) and anakinra (IL-1 receptor blocker). Beneficial for systemic JIA.

Abatacept: Blocks T-cell activation. Useful for polyarticular JIA.

Rituximab: Targets B cells. Reserved for severe cases resistant to other treatments.

3. Glucocorticoids:

- Can be given orally, intravenously, or directly into the joint (intra-articular).

- Used for rapid relief but not as a long-term solution due to side effects.

4. Non-pharmacologic Pain Management:

- Techniques like heat/cold applications, relaxation techniques, and distraction can help manage pain.
- **Regular Monitoring and Follow-up:**
 - **Ophthalmological Follow-up:** Regular eye exams are crucial as uveitis (eye inflammation) can develop in children with JIA.
 - **Regular Blood Tests:** Monitor for side effects of medications and disease activity.
 - **Periodic Imaging:** X-rays, MRIs to evaluate joint damage progression.
- **Surgical Intervention:**
 - In rare instances where significant joint damage has occurred, surgical procedures like joint replacement might be considered.
- **Psychosocial Support:**
 - Addressing the emotional and psychological needs of the child and family is paramount. Access to support groups, counseling, and educational resources can be beneficial.

Q: A) Disease modifying agents used for JIA ; B) Biological anti-TNF agents for JIA

A) Disease-Modifying Agents Used for Juvenile Idiopathic Arthritis (JIA)

- **Methotrexate**
 - First-line DMARD for most JIA subtypes
 - Dose: 10-15 mg/m²/week orally or subcutaneously
- **Sulfasalazine**
 - Used mainly for enthesitis-related and psoriatic JIA
 - Dose: 20-30 mg/kg/day in divided doses
- **Leflunomide**
 - Alternative to Methotrexate
 - Dose: 10-20 mg/day
- **Hydroxychloroquine**

- Used in mild cases or in combination
- Dose: 5 mg/kg/day
- **Azathioprine**
 - Less commonly used due to side effects
 - Dose: 1-3 mg/kg/day
- **Cyclosporine**
 - Used in severe, refractory cases
 - Dose: 2.5-5 mg/kg/day in divided doses

B) Biological Anti-TNF Agents for JIA

- **Etanercept**
 - Dose: 0.8 mg/kg/week subcutaneously, up to 50 mg/week
- **Infliximab**
 - Dose: 3-6 mg/kg IV at 0, 2, and 6 weeks, then every 4-8 weeks
- **Adalimumab**
 - Dose: 24 mg/m² body surface area up to 40 mg/dose every other week
- **Golimumab**
 - Dose: 50 mg subcutaneously once a month for patients >100 kg
- **Certolizumab Pegol**
 - Dose: 200 mg every 2 weeks or 400 mg every 4 weeks

Drug Name	Description	Dose	Adverse Effects
Methotrexate	First-line DMARD for most JIA subtypes	10-15 mg/m ² /week	Hepatotoxicity, Bone marrow suppression
Sulfasalazine	Used mainly for enthesitis-related and psoriatic JIA	20-30 mg/kg/day in divided doses	Gastrointestinal upset, Rash
Leflunomide	Alternative to Methotrexate	10-20 mg/day	Liver toxicity, Diarrhea

Hydroxychloroquine	Used in mild cases or in combination	5 mg/kg/day	Retinal toxicity, Rash
Azathioprine	Less commonly used due to side effects	1-3 mg/kg/day	Bone marrow suppression, Hepatotoxicity
Cyclosporine	Used in severe, refractory cases	2.5-5 mg/kg/day in divided doses	Nephrotoxicity, Hypertension
Etanercept	Anti-TNF agent	0.8 mg/kg/week, up to 50 mg/week	Infections, Injection site reactions
Infliximab	Anti-TNF agent	3-6 mg/kg IV at 0, 2, and 6 weeks	Infusion reactions, Infections
Adalimumab	Anti-TNF agent	24 mg/m ² up to 40 mg/dose every 2 weeks	Infections, Injection site reactions
Golimumab	Anti-TNF agent	50 mg subcutaneously once a month	Infections, Liver enzyme elevations
Certolizumab Pegol	Anti-TNF agent	200 mg every 2 weeks or 400 mg every 4 weeks	Infections, Hypersensitivity reactions

Biologic therapy in JIA

- ✚ Biologic therapy has revolutionized the treatment of Juvenile Idiopathic Arthritis (JIA), a heterogeneous group of autoimmune and inflammatory conditions in children.
- ✚ These therapies target specific components of the immune system to control inflammation, reduce symptoms, and prevent joint damage.

A. Types of Biologic Agents:

1. **Tumor Necrosis Factor (TNF) Inhibitors:** First line biologic agents for JIA. Include etanercept, adalimumab, and infliximab. Effective in reducing joint inflammation and preventing joint damage.

2. **Interleukin-1 (IL-1) Inhibitors:** Anakinra and canakinumab are used, particularly in systemic JIA and for those with macrophage activation syndrome.
3. **Interleukin-6 (IL-6) Inhibitors:** Tocilizumab is effective in systemic and polyarticular JIA. It can be used as a first-line biologic agent, especially in systemic JIA.
4. **T-cell Co-stimulation Modulator:** Abatacept is used in polyarticular JIA, particularly in patients who have had an inadequate response to TNF inhibitors.
5. **Janus Kinase (JAK) Inhibitors:** Tofacitinib is an oral agent used in older children with polyarticular JIA, particularly when there is an inadequate response to other biologics.

B. Indications for Use:

1. Biologics are typically considered in JIA when there is an inadequate response to first-line treatments like nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate.
2. Specific indications depend on the JIA subtype and severity of the disease.

C. Efficacy and Outcomes:

1. Biologics significantly improve symptoms, quality of life, and functional outcomes in JIA.
2. They have been shown to induce remission in a significant proportion of patients.
3. Early initiation of biologics may alter the disease course and prevent long-term joint damage.

D. Safety and Monitoring:

1. Regular monitoring for side effects is essential, including blood tests for liver function, blood counts, and immune function.

2. Increased risk of infections, including reactivation of latent tuberculosis.
3. Screening for tuberculosis and other infections is required before initiating therapy.
4. Vaccinations should be up to date, avoiding live vaccines while on biologic therapy.

E. Considerations in Treatment Choice:

1. The choice of biologic agent depends on JIA subtype, patient age, disease severity, comorbidities, and previous treatment responses.
2. Patient and family preferences, route of administration (injection vs. infusion), and cost considerations also play a role.

F. Long-Term Management:

1. JIA is a chronic condition, and long-term treatment may be necessary.
2. Regular follow-up with a pediatric rheumatologist to assess disease activity, adjust medications, and monitor for side effects.

Q: Systemic-onset Juvenile Idiopathic Arthritis (SOJIA)

It is one of the subsets of Juvenile Idiopathic Arthritis (JIA). It is characterized by both systemic and joint symptoms.

Definition:

- Arthritis in ≥ 1 joints accompanied by fever for at least 2 weeks.
- The fever should be documented to be daily (referred to as "quotidian") with at least two peaks daily for a minimum of 3 days.
- This is further accompanied by ≥ 1 of the subsequent symptoms:

Clinical Features:

- **Fever:** Distinctive pattern, twice daily peaks, lasting for at least 2 weeks.
- **Evanescient (nonfixed) erythematous rash:** Often salmon-colored and might last < 1 hour.
- **Generalized lymph node enlargement.**
- **Hepatomegaly or Splenomegaly or both:** Enlargement of the liver or spleen.

- **Serositis:** Manifesting as pericarditis, pleuritis, or peritonitis.

Epidemiology and Demographics:

- **Prevalence:** Constitutes 5-15% of all JIA patients.
- **Gender Distribution:** Roughly equal between males and females.
- **Peak Age of Onset:** Generally observed in children aged 1-5 years.

Additional Comments and Clinical Tips:

- **Skin Features:** Besides the typical rash, the Koebner phenomenon can be seen where lesions develop at sites of skin trauma.
- **Joint Involvement:** The arthritis can be polyarticular (involving many joints) and can potentially be destructive. Commonly involved joints include the knees, hips, cervical spine, and temporomandibular joint.
- **Laboratory Findings:**
 - Elevated Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) indicating inflammation.
 - Neutrophilic leukocytosis and thrombocytosis.
 - In severe cases, one may observe a decreased white blood cell count (suspect Macrophage Activation Syndrome or MAS).
 - Elevated ferritin levels.
- **ANA and RA Factor:** ANA is typically rare, and the Rheumatoid Factor (RA) is usually negative.
- **Treatment Considerations:** Patients with SOJIA may be less responsive to standard treatments like methotrexate (MTX). In resistant cases, considering the use of an IL-6 inhibitor may be beneficial.
- SOJIA, given its systemic manifestations, can sometimes be difficult to diagnose, especially in its early stages. Differential diagnoses can include infections, malignancies, and other rheumatologic conditions.
- IL-6 inhibitors have emerged as promising therapeutic agents for SOJIA, especially for patients who do not respond to traditional treatments.
- Close monitoring for Macrophage Activation Syndrome (MAS) is essential, especially in patients presenting with falling white blood cell counts and elevated ferritin.

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Q: A seven-year-old girl is admitted with pain and swelling of right knee and left ankle joint of two weeks' duration. Enumerate the likely causes. Discuss the differential diagnosis highlighting important pointers in history, examination and investigations

Likely Causes

- Septic Arthritis
- Juvenile Idiopathic Arthritis (JIA)
- Osteomyelitis
- Reactive Arthritis
- Rheumatic Fever
- Henoch-Schönlein Purpura (HSP)
- Systemic Lupus Erythematosus (SLE)
- Leukemia or other malignancies
- Lyme Disease
- Transient Synovitis
- Trauma or Injury

Differential Diagnosis: Important Pointers

Condition	History	Physical Examination	Investigations
Septic Arthritis	Acute onset, fever, localized pain	Warm, erythematous, limited ROM	Blood culture, joint aspiration, elevated WBC, CRP, ESR
JIA	Chronic joint pain, morning stiffness	Multiple joints involved, possible uveitis	Negative RF, ANA, normal to elevated ESR, CRP
Osteomyelitis	Fever, localized bone pain	Localized tenderness, possible erythema	MRI, bone biopsy, elevated WBC, ESR, CRP
Reactive Arthritis	History of recent infection	Asymmetric joint involvement, enthesitis	HLA-B27, negative joint cultures

Rheumatic Fever	Sore throat, fever	Migratory polyarthrititis, carditis	ASO titer, ECG, echocardiogram
HSP	Rash, abdominal pain	Palpable purpura, abdominal tenderness	Urinalysis, skin biopsy
SLE	Fatigue, malar rash	Joint involvement, malar rash, oral ulcers	ANA, anti-dsDNA, anti-Sm
Leukemia	Fatigue, easy bruising, night pains	Pallor, petechiae, hepatosplenomegaly	CBC, bone marrow biopsy
Lyme Disease	Tick exposure, erythema migrans	Mono or oligoarthrititis, erythema migrans	ELISA, Western blot
Transient Synovitis	Recent viral infection	Monoarthrititis, limited ROM	Normal to slightly elevated ESR, CRP
Trauma or Injury	History of fall or impact	Localized swelling, possible deformity	X-ray, CT scan

Note: ROM: Range of Motion

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Q: Macrophage Activation Syndrome (MAS) (in the Context of Rheumatic Diseases)

Definition

- Macrophage Activation Syndrome (MAS) is a severe, potentially life-threatening complication of rheumatic diseases, most commonly seen in systemic Juvenile Idiopathic Arthritis (sJIA). It is characterized by excessive activation and proliferation of T lymphocytes and macrophages, leading to overwhelming inflammation.

Pathophysiology

- Overactivation of the immune system, particularly macrophages and T cells.
- Excessive cytokine release, including interferon-gamma, TNF-alpha, and IL-6.
- Hemophagocytosis in bone marrow, spleen, and liver.

Clinical Features

- High, unremitting fever

- Splenohepatomegaly
- Lymphadenopathy
- Neurological symptoms like irritability, disorientation
- Hemorrhagic manifestations such as petechiae, purpura
- Jaundice

Laboratory Findings

- Pancytopenia
- Elevated liver enzymes
- Hyperferritinemia
- Elevated triglycerides
- Low fibrinogen
- Coagulopathy

Diagnostic Criteria

- Ferritin > 684 ng/mL
- Platelet count < $181 \times 10^9/L$
- AST > 48 U/L
- Triglycerides > 156 mg/dL
- Fibrinogen < 360 mg/dL

Treatment

- High-dose corticosteroids (e.g., methylprednisolone)
- Cyclosporine A
- Intravenous immunoglobulin (IVIG)
- Anakinra (IL-1 receptor antagonist)
- Etoposide in severe, refractory cases

Prognosis

- Highly variable, can be fatal if not promptly treated.
- Mortality rates have decreased with early recognition and aggressive treatment but remain significant.

Prevention

- Close monitoring of sJIA patients for early signs of MAS.
- Prophylactic treatment with medications like Anakinra in high-risk patients.

Table: MAS for Quick Reference

Section	Key Points
Pathophysiology	Overactivation of immune cells, excessive cytokine release, hemophagocytosis
Clinical Features	High fever, hepatosplenomegaly, lymphadenopathy, neurological symptoms
Laboratory Findings	Pancytopenia, elevated liver enzymes, hyperferritinemia
Diagnostic Criteria	Specific levels of ferritin, platelet count, AST, triglycerides, fibrinogen
Treatment	Corticosteroids, Cyclosporine A, IVIG, Anakinra, Etoposide
Prognosis	Variable, can be fatal
Prevention	Monitoring, prophylactic treatment

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Q: SLE-Diagnostic criteria

- Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens.

Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus 2012*

Sensitivity and Specificity: Higher sensitivity (93% vs 77%) but lower specificity (85% vs 99%) than the ACR criteria

The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE.

CLINICAL CRITERIA

- Acute cutaneous lupus

- Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus
- Chronic cutaneous lupus
- Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
- Oral or nasal ulcers
- Nonscarring alopecia
- Synovitis (≥ 2 joints)
- Serositis
- Pleurisy or pericardial pain ≥ 1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis
- Renal
- Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hr
- Neurologic
- Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state
- Hemolytic anemia
- Leukopenia ($<4,000/\text{mm}^3$) or lymphopenia ($<1,000/\text{mm}^3$)
- Thrombocytopenia ($<100,000/\text{mm}^3$)

IMMUNOLOGIC CRITERIA

- Positive antinuclear antibody
- Positive double-stranded DNA antibody
- Positive anti-Smith antibody
- Antiphospholipid antibody positivity
- Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high-titer anticardiolipin antibody level
- (IgA, IgG, IgM), or positive anti- $\beta 2$ -glycoprotein-1 antibody (IgA, IgG, IgM)
- Low complement
- Low C3, C4, or CH50 level
- Positive direct Coombs test

American College of Rheumatology (ACR) 1997 Revised Classification Criteria

The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

- **Malar Rash:** Butterfly-shaped rash over cheeks and nose
- **Discoid Rash:** Raised red patches
- **Photosensitivity:** Skin rash as a reaction to sunlight
- **Oral or Nasal Ulcers:** Usually painless
- **Arthritis:** Nonerosive arthritis involving two or more peripheral joints
- **Serositis:** Pleuritis, pericarditis, or peritonitis
- **Renal Manifestations:** Persistent proteinuria or renal casts
- **Hematologic Manifestations:** Hemolytic anemia, leukopenia ($<4,000$ leukocytes/mm³), lymphopenia ($<1,500$ leukocytes/mm³), thrombocytopenia ($<100,000$ thrombocytes/mm³)
- **Immunologic Abnormalities:** Positive anti-double-stranded DNA or anti-Smith antibody, false-positive rapid plasma reagin test result, positive lupus anticoagulant test result, or elevated anticardiolipin IgG or IgM antibody
- **Positive Antinuclear Antibody Test Result:** A positive ANA test is very sensitive for SLE but not very specific.

Q: Cutaneous Manifestations of Lupus Erythematosus

- Lupus Erythematosus (LE) is an autoimmune disease with a wide range of clinical manifestations, including various cutaneous features.

Types of Cutaneous Manifestations

1. Malar Rash

- Butterfly-shaped rash over cheeks and nose
- Often photosensitive

2. Discoid (Annular) Rash

- Raised, red patches
- More chronic and may lead to scarring

3. Photosensitive Rash

- Skin rash triggered by exposure to sunlight

4. **Cutaneous Vasculitis**

- Petechiae, palpable purpura, digit ulcers, gangrene, urticaria

5. **Livedo Reticularis**

- Mottled reticular pattern observed primarily on the skin

6. **Periungual Capillary Abnormalities**

- Changes in the small blood vessels around the nails

7. **Raynaud Phenomenon**

- Spasm of blood vessels in response to cold or stress

8. **Alopecia**

- Hair loss, often in patches

9. **Oral and Nasal Ulcers**

- Usually painless

10. **Panniculitis**

- Inflammation of the subcutaneous fat

11. **Chilblains**

- Inflammatory skin condition occurring in response to cold weather

12. **Subacute Cutaneous Lupus**

- Presents as non-scarring, non-atrophy-producing, photosensitive dermatosis

13. **Chronic Cutaneous Lupus**

- Includes classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap

Differential Diagnosis

- Dermatomyositis
- Scleroderma
- Eczema
- Psoriasis

- Vasculitis

Management

- Topical corticosteroids for localized lesions
- Antimalarial drugs like hydroxychloroquine for more generalized skin involvement
- Systemic corticosteroids for severe cutaneous manifestations
- Immunosuppressive agents like azathioprine or methotrexate for refractory cases

Table:

Cutaneous Manifestation	Clinical Features	Differential Diagnosis	Management
Malar Rash	Butterfly-shaped, often photosensitive	Rosacea, Dermatomyositis	Topical corticosteroids
Discoid Rash	Raised, red patches, may scar	Psoriasis, Eczema	Antimalarials, Topical corticosteroids
Photosensitive Rash	Triggered by sunlight	Photodermatitis	Sunscreen, Antimalarials
Cutaneous Vasculitis	Petechiae, palpable purpura	Henoch-Schönlein purpura, Vasculitis	Systemic corticosteroids
Livedo Reticularis	Mottled reticular pattern	Vasculopathy	Supportive care
Alopecia	Hair loss	Androgenic alopecia, Alopecia areata	Topical Minoxidil

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Q: How do you classify and treat lupus nephritis

Classification and Treatment of Lupus Nephritis

Classification

- **Class I:** Minimal Mesangial Lupus Nephritis
 - Histologically normal glomeruli
- **Class II:** Mesangial Proliferative Lupus Nephritis

- Mesangial cell proliferation and matrix expansion
- **Class III:** Focal Lupus Nephritis
 - Segmental glomerular involvement
- **Class IV:** Diffuse Proliferative Lupus Nephritis
 - Most severe form; diffuse glomerular involvement
- **Class V:** Membranous Lupus Nephritis
 - Thickening of glomerular basement membrane
- **Class VI:** Advanced Sclerosing Lupus Nephritis
 - Sclerosis of more than 90% of glomeruli

Treatment

Induction Therapy

- **Cyclophosphamide:** 500-1000 mg/m² IV monthly
- **Mycophenolate Mofetil (MMF):** 600 mg/m², up to 1500 mg, twice daily
- **Glucocorticoids:** Various regimens

Maintenance Therapy

- **Cyclophosphamide:** Every 3 months
- **MMF:** Continued
- **Azathioprine:** Alternative to MMF

Other Agents

- **Rituximab:** For treatment-resistant cases
- **Belimumab:** FDA-approved for lupus in adults

Special Considerations

- **Pediatric SLE:** Specific treatment plans advised by the Childhood Arthritis Rheumatology Research Alliance (CARRA) for class IV lupus nephritis and certain patients with class III, V, or VI.

Table: Treatment Options for Lupus Nephritis

Classification	Induction Therapy	Maintenance Therapy	Other Agents

Class I-III	MMF + Steroids	MMF or Azathioprine	Rituximab
Class IV-VI	Cyclophosphamide + Steroids	Cyclophosphamide	Belimumab

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Q: Clinical Features of Juvenile Dermatomyositis

- Juvenile Dermatomyositis (JDM) is a rare inflammatory myopathy affecting children, characterized by proximal muscle weakness and a distinct rash.

Clinical Manifestations

- Muscle Weakness:**
 - Proximal muscle involvement
 - 90-100% of cases
- Skin Lesions:**
 - Heliotrope rash of eyelids (66-95%)
 - Gotttron papules (57-95%)
 - Erythematous rash of malar/facial area (42-100%)
- Muscle Pain and Tenderness:**
 - Present in 30-75% of cases
- Dysphagia or Dysphonia:**
 - Occurs in 13-40% of cases
- Arthritis and Arthralgia:**
 - Observed in 22-58% of cases
- Fever:**
 - Noted in 16-65% of cases
- Gastrointestinal Signs and Symptoms:**
 - Present in 8-37% of cases
- Cardiac Involvement:**

- Rare, occurring in 0-3% of cases
- **Calcinosis:**
 - Observed in 12-30% of cases
- **Lipodystrophy:**
 - Occurs in 11-14% of cases

Differential Diagnosis

- Eczema
- Psoriasis
- Erythema nodosa
- Malar rash from SLE
- Muscular dystrophies (e.g., Duchenne, Becker)

Diagnostic Criteria

- Heliotrope rash of the eyelids
- Gottron papules
- Plus 3 of the following:
 - Weakness (Symmetric, Proximal)
 - Muscle enzyme elevation
 - Electromyographic changes
 - Muscle biopsy findings

Table: Clinical Features of Juvenile Dermatomyositis

Clinical Feature	Frequency (%)	Remarks
Muscle Weakness	90-100	Proximal muscles affected
Heliotrope Rash	66-95	Eyelids
Gottron Papules	57-95	Over joints
Muscle Pain	30-75	Varies in intensity
Dysphagia	13-40	Difficulty in swallowing

Arthritis	22-58	Joint involvement
Fever	16-65	Variable
Calcinosis	12-30	Calcium deposits in tissues

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Q: Diagnosis and management of juvenile dermatomyositis

Juvenile Dermatomyositis (JDM) is a rare and complex autoimmune disease in children, characterized by inflammation of the muscles and skin.

1. Clinical Features for Diagnosis:

1. **Muscle Weakness:** Proximal muscle weakness, often symmetric, affecting shoulders, hips, and thighs.
2. **Skin Rash:** Characteristic rashes including Gottron's papules (raised, scaly bumps over knuckles, elbows, knees) and heliotrope rash (violet discoloration on eyelids).
3. **Systemic Symptoms:** Fever, fatigue, and malaise.
4. **Other Features:** Difficulty swallowing, abdominal pain, lung involvement (interstitial lung disease).

2. Diagnostic Evaluation:

1. **Laboratory Tests:** Elevated muscle enzymes (Creatine Kinase [CK], Aldolase, AST, ALT, LDH).
2. **Autoantibodies:** Anti-nuclear antibodies (ANA), myositis-specific antibodies (e.g., anti-Mi-2, anti-MDA5).
3. **Muscle Biopsy:** Shows evidence of muscle inflammation, fiber necrosis, and capillary changes.
4. **Magnetic Resonance Imaging (MRI):** Identifies muscle inflammation and edema.

5. **Electromyography (EMG):** Detects abnormal electrical activity in muscles.

6. **Pulmonary Function Tests:** Assess for lung involvement.

3. Management Strategies:

1. **Corticosteroids:** Prednisone is the first-line treatment to reduce inflammation.
2. **Steroid-Sparing Agents:** Methotrexate or azathioprine to reduce steroid side effects and maintain remission.
3. **Biologic Agents:** Rituximab, IVIG (intravenous immunoglobulin) for refractory cases.
4. **Calcineurin Inhibitors:** Tacrolimus or cyclosporine, particularly in cases with severe muscle or skin involvement.
5. **Physical Therapy:** To maintain muscle strength and function.
6. **Skin Care:** Sun protection, topical corticosteroids, and emollients for skin rashes.
7. **Nutritional Support:** Diet rich in protein and calcium, vitamin D supplementation.
8. **Regular Monitoring:** For disease activity, treatment side effects, and growth in children.

4. Complications and Monitoring:

1. **Calcium Deposits (Calcinosis):** In muscles, skin, and subcutaneous tissues.
2. **Gastrointestinal Ulcers and Bleeding:** Due to steroid use.
3. **Growth and Developmental Delay:** Secondary to chronic inflammation and long-term steroid use.
4. **Increased Risk of Infections:** Due to immunosuppressive therapy.

5. Patient and Family Education:

1. Educating about the disease, treatment plan, and importance of medication adherence.

2. Guidance on lifestyle modifications, including physical activity and sun protection.

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Q: Clinical Features/presentation of Kawasaki Disease

- Kawasaki Disease (KD) is an acute, systemic vasculitis that predominantly affects children.
- It is characterized by inflammation of medium-sized arteries, particularly the coronary arteries.

Clinical Manifestations

Classic Clinical Criteria

- **Fever:**
 - Persistent for at least 5 days
 - Often high and remittent
- **Changes in Extremities:**
 - Acute Phase: Erythema of palms and soles, edema of hands and feet
 - Subacute Phase: Periungual peeling of fingers and toes during weeks 2 and 3
- **Polymorphous Exanthem:**
 - Variable rash that can be maculopapular, erythema multiforme-like, or scarlatiniform
- **Bilateral Bulbar Conjunctival Injection:**
 - Without exudate
 - Spares limbus
- **Oral and Pharyngeal Changes:**
 - Erythema and cracking of lips
 - Strawberry tongue

- Erythema of oral and pharyngeal mucosa
- **Cervical Lymphadenopathy:**
 - Greater than 1.5 cm in diameter
 - Usually unilateral and in the anterior cervical triangle

Additional Clinical and Laboratory Findings

- **Cardiovascular System:**
 - Myocarditis
 - Pericarditis
 - Valvular regurgitation
 - Coronary artery abnormalities
 - Aneurysms of medium-sized noncoronary arteries
- **Respiratory System:**
 - Not a primary feature but can have respiratory symptoms
- **Laboratory Findings:**
 - Hypoalbuminemia
 - Hyponatremia
 - Thrombocytosis after the first week
 - Sterile pyuria
 - Elevated serum transaminases

Table: Clinical Features of Kawasaki Disease

Clinical Feature	Description
Fever	Lasting at least 5 days
Changes in Extremities	Erythema and edema in acute phase
Polymorphous Exanthem	Variable skin rash
Conjunctival Injection	Bilateral, without exudate
Oral Changes	Strawberry tongue, erythema of oral mucosa

Cervical Lymphadenopathy	>1.5 cm, usually unilateral
Cardiovascular Involvement	Myocarditis, pericarditis, coronary abnormalities
Additional Lab Findings	Hypoalbuminemia, hyponatremia, elevated transaminases

Table: Other clinical findings in KD

System	Clinical Findings of KD
Cardiovascular System (CVS)	Pancarditis Shock, Peripheral gangrene Coronary artery abnormalities & Aneurysms of medium-sized noncoronary arteries Aortic root enlargement
Respiratory System	Peribronchial and interstitial infiltrates on chest radiograph Pulmonary nodules
Musculoskeletal System	Arthritis, arthralgias (pleocytosis of synovial fluid)
Gastrointestinal Tract	Diarrhea, vomiting, abdominal pain Hepatitis, jaundice Hydrops of gallbladder Pancreatitis
Central Nervous System	Extreme irritability Aseptic meningitis (pleocytosis of cerebrospinal fluid) Facial nerve palsy Sensorineural hearing loss
Genitourinary System	Urethritis, hydrocele

Other Findings	Desquamating rash in groin Retropharyngeal phlegmon Anterior uveitis by slit-lamp examination Erythema, induration at BCG inoculation site/ Reactivation of BCG scar
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Q: Phases of Kawasaki Disease

- Kawasaki Disease (KD) is an acute febrile illness primarily affecting children.
- It is a systemic vasculitis with a predilection for coronary arteries.

Clinical Phases

Acute Febrile Phase

- **Duration:** Usually lasts up to 2 weeks.
- **Characteristics:**
 - High fever
 - Other acute signs such as rash, conjunctival injection, and extremity changes
- **Laboratory Findings:**
 - Elevated CRP
 - Leukocytosis
- **Cardiac Involvement:**
 - Risk of coronary artery abnormalities

Subacute Phase

- **Duration:** Starts when fever subsides and lasts until clinical signs disappear.
- **Characteristics:**
 - Desquamation of fingers and toes
 - Thrombocytosis

- **Cardiac Involvement:**
 - Risk of thrombosis in coronary aneurysms
- **Laboratory Findings:**
 - Normalizing inflammatory markers

Convalescent Phase

- **Duration:** Starts when all clinical signs have disappeared and lasts until ESR returns to normal.
- **Characteristics:**
 - No acute symptoms
 - May have lingering fatigue
- **Laboratory Findings:**
 - Normal ESR
 - Normal CRP

Table: Phases of Kawasaki Disease

Phase	Duration	Characteristics	Laboratory Findings	Cardiac Involvement
Acute Febrile	Up to 2 weeks	High fever, rash, conjunctival injection	Elevated CRP, Leukocytosis	Risk of coronary artery abnormalities
Subacute	Fever subsides to signs disappear	Desquamation, thrombocytosis	Normalizing markers	Risk of thrombosis in aneurysms
Convalescent	Signs disappear to ESR normal	No acute symptoms, possible fatigue	Normal ESR, Normal CRP	None

Pathological Processes of KD Arteriopathy:

Phase	Description
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1st phase	Necrotizing arteritis (1st 2 wk) Neutrophilic process Saccular aneurysms may form
2nd phase	Subacute/chronic vasculitis Driven by lymphocytes, plasma cells, and eosinophils May last weeks to years
3rd Phase	Luminal myofibroblastic proliferation (LMP) Develop smooth muscle cell myofibroblasts Which cause progressive stenosis

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Q: Diagnostic Criteria for Kawasaki Disease (KD)

- Kawasaki Disease is a systemic vasculitis primarily affecting children.
- It has significant cardiac implications, including the potential for coronary artery abnormalities.

Epidemiologic Case Definition (Classic Clinical Criteria)

- **Fever:** Persisting for at least 5 days.
- **Principal Features:** Presence of at least 4 of the following:
 - Changes in extremities
 - Acute: Erythema of palms, soles; edema of hands, feet
 - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
 - Polymorphous exanthem
 - Bilateral bulbar conjunctival injection without exudate
 - Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
 - Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
- **Exclusion:** Other diseases with similar findings should be excluded.

Other Clinical and Laboratory Findings

- **Cardiovascular System:** Myocarditis, pericarditis, valvular regurgitation, shock, coronary artery abnormalities, etc.
- **Respiratory System:** Abnormal plasma lipids, hypoalbuminemia, hyponatremia, etc.
- **Additional Lab Findings:** Thrombocytosis after week 1, sterile pyuria, elevated serum transaminases, etc.

Special Considerations

- Patients with fever for at least 5 days and fewer than 4 principal criteria can be diagnosed with KD when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.
- In the presence of ≥ 4 principal criteria, KD diagnosis can be made on day 4 of illness.

Table: Diagnostic Criteria for Kawasaki Disease

Criteria Type	Features
Fever	Persisting for at least 5 days
Principal Features	At least 4 of the following: Changes in extremities, exanthem, conjunctival injection, etc.
Exclusion Criteria	Other diseases with similar findings should be excluded
Additional Lab Findings	Thrombocytosis after week 1, sterile pyuria, elevated serum transaminases, etc.
Special Considerations	Diagnosis can be made on day 4 if ≥ 4 principal criteria are present

Definitions:

- **Complete KD:**
 - Patients with fever of at least 5-day duration.
 - Presence/history of 4 or more of the 5 principal clinical findings.
 - These cases are labelled as typical or classic KD.
- **Incomplete KD:**

- Presence of fever with less than 4 out of the 5 principal clinical criteria.
- Compatible laboratory or echocardiography findings suggest incomplete KD.
- Often seen in infants <6 months and children >6 years of age.
- The incomplete clinical picture often delays the diagnosis.
- **Atypical KD:**
 - Patients who, along with the usual clinical features of KD, also have few unusual clinical manifestations.
 - Unusual manifestations include pulmonary involvement and renal impairment.
 - These cases are diagnosed to have atypical KD.

Q: Differential Diagnosis of Kawasaki Disease (KD)

- Kawasaki Disease (KD) is a systemic vasculitis affecting children, often leading to coronary artery abnormalities.

Table: Differential Diagnosis of Kawasaki Disease

Category	Conditions
Viral Infections	Adenovirus; Enterovirus; Measles; Epstein-Barr virus; Cytomegalovirus
Bacterial Infections	Scarlet fever; Rocky Mountain spotted fever; Leptospirosis; Bacterial cervical lymphadenitis ± retropharyngeal phlegmon; Meningococemia; Urinary tract infection
Rheumatologic Disease	Systemic-onset juvenile idiopathic arthritis; Behçet disease; Rheumatic fever
Other	Toxic shock syndromes; Serum sickness; Staphylococcal scalded skin syndrome; Macrophage activation syndrome; Drug hypersensitivity reactions; Stevens-Johnson syndrome; Aseptic meningitis

Key Points

- **Viral Infections:** Detection of a virus does not exclude KD if principal clinical features are present.

- **Bacterial Infections:** Conditions like scarlet fever and Rocky Mountain spotted fever can mimic KD but usually have distinguishing features.
- **Rheumatologic Diseases:** Conditions like systemic-onset juvenile idiopathic arthritis may present similarly but have different treatment protocols.
- **Other Conditions:** Toxic shock syndromes, serum sickness, and other conditions may mimic KD but are usually distinguishable based on clinical and laboratory findings.

Clinical Implications

- Misdiagnosis can lead to inappropriate treatment and increased risk of coronary artery abnormalities.
- A thorough evaluation is essential for distinguishing KD from other conditions that present with similar symptoms.

Features against KD:

Characteristics suggesting that another diagnosis should be considered include:

- Exudative conjunctivitis
- Exudative pharyngitis
- Ulcerative intraoral lesions
- Bullous or vesicular rash
- Generalized adenopathy
- Splenomegaly

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Q: Pathogenesis of Kawasaki Disease (KD)

- Kawasaki Disease (KD) is an acute febrile illness primarily affecting children.
- It is a systemic inflammatory disorder that manifests as vasculitis, particularly targeting the coronary arteries.

Etiology

- The exact cause of KD remains unknown.
- Epidemiologic and clinical features suggest a possible infectious origin.

Pathophysiological Mechanisms

1. Systemic Inflammation

- KD is a systemic inflammatory disorder that manifests as vasculitis.

2. **Coronary Artery Involvement**

- A predilection for coronary arteries is observed.
- 20-25% of untreated children develop coronary artery abnormalities (CAA), including aneurysms.

3. **Immune System Activation**

- Excessive activation of T lymphocytes and macrophages.

4. **Cytokine Release**

- Overproduction of cytokines like interferon-gamma, TNF-alpha, and IL-6.

5. **Hemophagocytosis**

- Occurs in bone marrow, spleen, and liver.

6. **Necrotizing Arteritis**

- Destruction of intima, elastica interna, media, and variably, adventitia leading to aneurysm formation.

Clinical Implications

- KD is the leading cause of acquired heart disease in children in developed countries.
- Early diagnosis and treatment are crucial to prevent coronary artery abnormalities.
- Predominantly affects the medium-size arteries.
- The coronary arteries are the most commonly involved
- In order of highest to lowest frequency of occurrence, typical sites of coronary artery aneurysms include→
 - Proximal LAD and proximal RCA > Left main coronary artery (LMCA) > Left circumflex, distal RCA
- There is typical intimal proliferation and infiltration of the vessel wall with mononuclear cells.
- Beadlike aneurysms and thromboses may be seen along the artery.
- Other manifestations include pericarditis, myocarditis, myocardial ischemia and infarction %and cardiomegaly.
- Kobayashi score is the most widely used and has high sensitivity and specificity

Prognosis

- KD can lead to long-term cardiovascular complications if not treated promptly.

Pathological Processes of KD Arteriopathy:

Phase	Description
1st phase	Necrotizing arteritis (1st 2 wk) Neutrophilic process Saccular aneurysms may form
2nd phase	Subacute/chronic vasculitis Driven by lymphocytes, plasma cells, and eosinophils May last weeks to years
3rd Phase	Luminal myofibroblastic proliferation (LMP) Develop smooth muscle cell myofibroblasts Which cause progressive stenosis

Q: Complications of Kawasaki Disease (KD)

- Kawasaki Disease (KD) is an acute febrile illness primarily affecting children 5-15yrs.
- It is a systemic vasculitis with a predilection for coronary arteries.

Cardiovascular Complications

- **Myocarditis and Pericarditis:** Inflammation of the heart muscle and pericardium.
- **Valvular Regurgitation:** Dysfunction of heart valves leading to backflow of blood.
- **Coronary Artery Abnormalities (CAA):** Including aneurysms, stenosis, and thrombosis.
- **Aortic Root Enlargement:** Expansion of the aortic root, increasing the risk for aortic dissection.

- **Peripheral Gangrene:** Necrosis in peripheral tissues due to impaired blood supply.
- **Shock:** Severe hypotension and tissue hypoxia.
- Aneurysms of medium-sized noncoronary arteries

Cardiovascular Collapse in K.D:

- 5% children
- Hypotension requiring the initiation of volume expanders, the infusion of vasoactive agents
- Thrombocytopenia and coagulopathy common
- Differential: Bacterial sepsis

Higher risk of:

- IVIG resistance
- CA abnormalities
- MR
- Prolonged myocardial dysfunction
- Respiratory Complications
- **Respiratory Symptoms:** Such as rhinorrhea or cough, occur in 35% of patients.

Other Clinical and Laboratory Findings

- **Gastrointestinal Symptoms:** Such as vomiting, diarrhea, or abdominal pain, occur in >60% of patients.
- **Exudative Conjunctivitis, Pharyngitis:** Inflammation of the eye and throat.
- **Generalized Lymphadenopathy:** Swelling of lymph nodes throughout the body.
- **Splenomegaly:** Enlarged spleen.
- **Bullous, Petechial, or Vesicular Rashes:** Various types of skin rashes.

Prognosis

- **Morbidity and Mortality:** Almost all the morbidity and mortality in KD occur in patients with large or giant coronary artery aneurysms.

Cause of death:

Early phase – severe myocarditis

Late phase – coronary artery aneurysm rupture

Clinical Implications

- Early diagnosis and treatment are crucial to prevent these complications.
- KD is the leading cause of acquired heart disease in children in developed countries.

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Q: Echocardiography in Kawasaki Disease (KD)

- Echocardiography is a pivotal diagnostic and monitoring tool in the management of Kawasaki Disease (KD).
- KD is a systemic vasculitis that predominantly affects coronary arteries, making cardiovascular assessment crucial.

Indications for Echocardiography

- **Initial Diagnosis:** Performed at the time of diagnosis to assess coronary artery status.
- **Monitoring:** Repeated 1-2 weeks after the onset of illness.
- **Recurrent Symptoms:** More frequent studies may be necessary if symptoms recur or initial studies are abnormal.

Parameters Assessed

1. **Coronary Artery Abnormalities (CAA)**
 - Detection of aneurysms, stenosis, and thrombosis.
2. **Left Ventricular Function**
 - Assessment of myocardial contractility and ejection fraction.
3. **Valvular Regurgitation**
 - Evaluation of mitral and aortic valve function.
4. **Pericardial Effusion**
 - Identification of fluid accumulation around the heart.

Interpretation and Clinical Implications

1. **Normal Echocardiography**

- If initial studies are normal, a repeat study should be performed 6-8 weeks after the onset of illness.

2. **Abnormal Findings**

- Tailored cardiology follow-up is warranted based on the patient's coronary status.

3. **Long-term Monitoring**

- For patients without CAA at any time during the illness, echocardiography and a lipid profile are recommended 1 year later.
- Periodic evaluation for preventive cardiology counseling is advised.

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Q: Algorithmic approach to a suspected case of Kawasaki disease

Evaluation of Suspected Incomplete Kawasaki Disease:

- **Starting Point:**
 - Children with a fever for ≥ 5 days and 2 or 3 compatible clinical criteria.
 - OR infants with a fever for ≥ 7 days without any other explanation.
- 1. **Initial Laboratory Assessment:**
 - Assess laboratory tests, specifically:
 - CRP (C-reactive protein) level
 - ESR (Erythrocyte Sedimentation Rate)
- 2. **Lab Results Classification:**
 - If CRP is < 3.0 mg/dL and ESR is < 40 mm/hr:
 - Move to further clinical and laboratory evaluation.
 - If CRP is ≥ 3.0 mg/dL and/or ESR is ≥ 40 mm/hr:
 - Check for 3 or more of the following laboratory findings:
 1. Anemia for age
 2. Platelet count of $\geq 450,000$ after the 7th day of fever
 3. Albumin ≤ 3.0 g/dL
 4. Elevated ALT level (Alanine Transaminase, a liver enzyme)

5. WBC (White Blood Cell) count of $\geq 15,000/\text{mm}^3$
6. Urine ≥ 10 WBC/hpf (White Blood Cells per high power field)

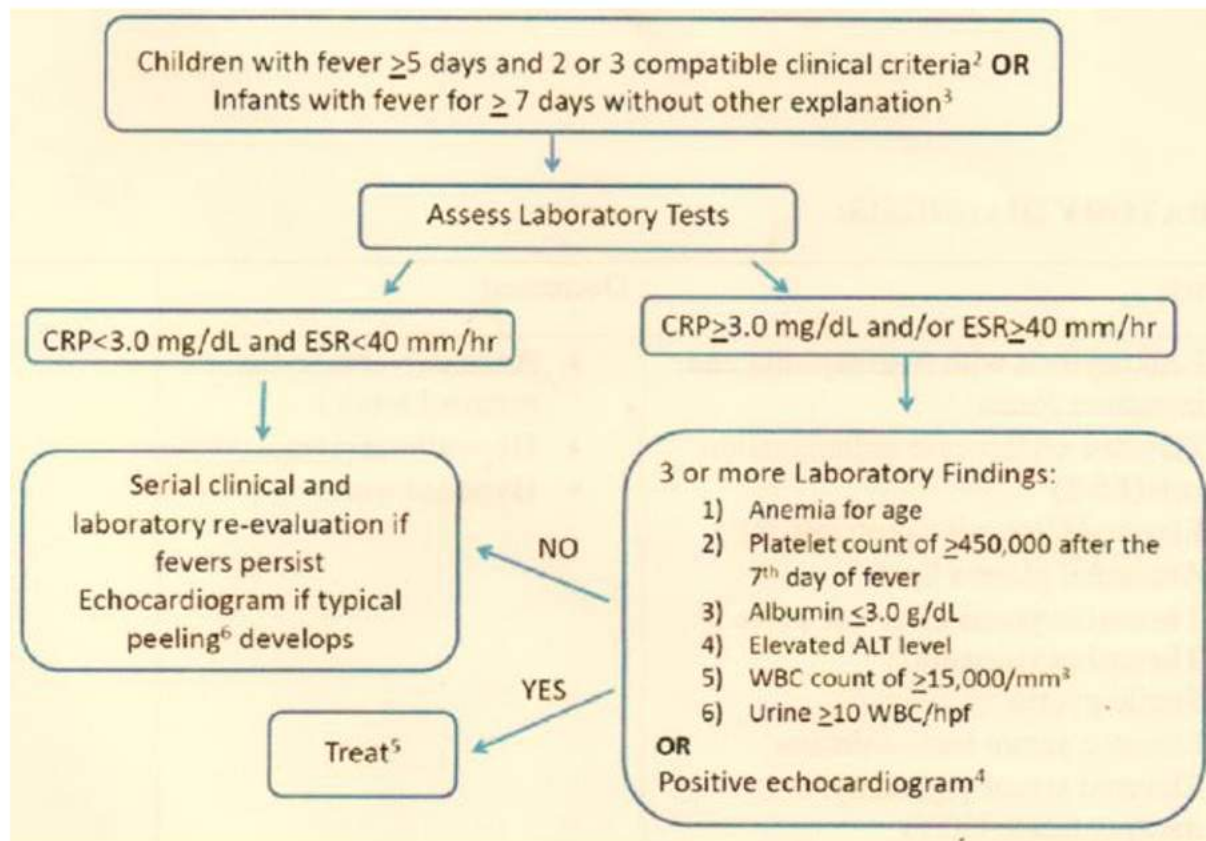
- Additionally, look for any positive echocardiogram findings.

3. **Further Clinical and Laboratory Evaluation:**

- If echocardiogram shows typical "peeling" development, the patient should be treated for KD.

4. **Treatment Decision:**

- If the findings and symptoms align with the KD criteria, then the patient should undergo treatment.



Initial Echocardiography is considered positive for purposes evaluation if any of 3 conditions are met:

1. Coronary artery aneurysm is observed; or
2. Z score of left anterior descending coronary artery or right coronary artery > 2.5 ;

3. 3 or more other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5 z.

Note:

If the echocardiogram is positive, treatment should be given within 10 days of fever onset

or

after the tenth day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation

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Q: Treatment of Kawasaki Disease (KD)

- Kawasaki Disease (KD) is an acute febrile vasculitis that predominantly affects children.
- Early treatment is crucial to prevent coronary artery abnormalities and other complications.

Acute Stage Treatment

- **Intravenous Immune Globulin (IVIG):** 2 g/kg over 10-12 hours.
 - Adverse Effects: Headache, chills, myalgia, transient neutropenia
- **Aspirin:** Dose: High-dose (80-100 mg/kg/day) divided every 6 hours orally until the patient is afebrile for at least 48 hours.
 - then low-dose (3-5 mg/kg/day) for antiplatelet effect to continue
 - Adverse Effects: Gastrointestinal upset, Reye's syndrome in viral illnesses

Treatment for IVIG-Resistant Patients

- **Second Infusion of IVIG:** 2 g/kg IV.
- **IVIG + Prednisolone:** IVIG 2 g/kg IV + prednisolone 2 mg/kg/day IV divided every 8 hours until afebrile, then orally until CRP normalized.
- **Infliximab:** Single infusion of 5 mg/kg IV given over 2 hours.
- **Alternative Treatments:** Cyclosporine, Anakinra, Cyclophosphamide, Plasma exchange.

- **Adjunctive Therapies:**
 - **Clopidogrel or Dipyridamole:**
 - Description: Antiplatelet agents
 - Dose: Variable depending on age and weight
 - Adverse Effects: Bleeding risk, gastrointestinal upset
 - **Warfarin:**
 - Description: Anticoagulant
 - Dose: Adjusted to maintain INR 2-3
 - Adverse Effects: Bleeding risk, requires regular monitoring
- **Supportive Care:**
 - **Antipyretics:**
 - Description: Fever control (other than aspirin)
 - Dose: Paracetamol 10-15 mg/kg every 4-6 hours as needed
 - Adverse Effects: Hepatotoxicity in overdose
 - **Fluid and Electrolyte Management:**
 - Description: Maintenance of hydration and electrolyte balance
 - Dose: Individualized
 - Adverse Effects: Fluid overload if not monitored
- **Monitoring and Follow-up:**
 - Echocardiography at diagnosis, 1-2 weeks, and 4-6 weeks
 - Regular pediatric and cardiology follow-up
 - To assess coronary artery status and other cardiac parameters.
- **Laboratory Tests:** To monitor inflammatory markers and other relevant parameters.

Special Considerations

- Treatment should ideally be administered within 10 days of disease onset.

- For patients diagnosed after the 10th day of fever with persistent symptoms, strong consideration should be given to treatment.

Prognosis

- Treatment results in defervescence and resolution of clinical signs in approximately 85% of patients.
- The prevalence of coronary disease is <5% in those treated with IVIG and aspirin within the first 10 days of illness.

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Q: Role of salicylates in Kawasaki disease

- **Role in Treatment:**
 - **Anti-Inflammatory:** Salicylates like aspirin exert potent anti-inflammatory effects, which are crucial in managing the systemic inflammation in Kawasaki disease.
 - **Antipyretic:** Effective in reducing the fever associated with Kawasaki disease.
 - **Antiplatelet:** Low-dose aspirin is used to prevent thrombosis by inhibiting platelet aggregation, a significant concern given the risk of coronary artery aneurysms in Kawasaki disease.
- **Dosing Regimen:**
 - **High-Dose Phase:** Initially, high doses (80-100 mg/kg/day divided into four doses) are administered until the fever subsides.
 - **Low-Dose Phase:** After fever resolution, the dose is reduced to antiplatelet levels (3-5 mg/kg/day) and is continued until the risk of thrombosis is minimized, often several weeks or until coronary artery abnormalities have resolved.
- **Monitoring:**
 - Regular liver function tests, complete blood counts, and renal function tests are advised due to the potential adverse effects.
 - Monitoring for Reye's syndrome, especially if there are signs of a viral infection.
- **Adverse Effects:**

- **Gastrointestinal:** Gastric irritation, ulceration, and bleeding.
- **Hematological:** Increased bleeding tendency.
- **Metabolic:** Reye's syndrome, particularly when administered during viral infections.
- **Hepatic:** Elevated liver enzymes, especially when used in high doses for prolonged periods.
- **Contraindications and Precautions:**
 - Contraindicated in patients with known hypersensitivity to salicylates.
 - Use with caution in patients with pre-existing liver or kidney disease.
- **Adjunct to Other Therapies:**
 - Usually used in conjunction with Intravenous Immunoglobulin (IVIG) for synergistic effects on inflammation and immune modulation.

Q: Classification of Vasculitis Based on Size of Involved Vessels

- Vasculitis is a heterogeneous group of disorders characterized by inflammation of blood vessels.
- Classification based on the size of the involved vessels provides a structured approach to diagnosis and management.
- This classification is based on the Chapel Hill Consensus Conference (CHCC) nomenclature and is widely used for the categorization of vasculitides.

Large Vessel Vasculitis

- **Examples:**
 - Takayasu Arteritis
 - Giant Cell Arteritis

Medium Vessel Vasculitis

- **Examples:**
 - Polyarteritis Nodosa
 - Kawasaki Disease

Small Vessel Vasculitis

- **ANCA-Associated Small Vessel Vasculitis**
 - Microscopic Polyangiitis
 - Granulomatosis with Polyangiitis
 - Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)
- **Immune Complex Small Vessel Vasculitis**
 - Anti-glomerular basement membrane (anti-GBM) disease
 - IgA Vasculitis (Henoch-Schönlein Purpura)
 - Hypocomplementemic Urticarial Vasculitis

Variable Vessel Vasculitis

- **Examples:**
 - Behçet Disease
 - Cogan Syndrome

Single-Organ Vasculitis

- **Examples:**
 - Cutaneous Leukocytoclastic Vasculitis
 - Cutaneous Arteritis
 - Primary Central Nervous System Vasculitis
 - Isolated Aortitis

Vasculitis Associated with Systemic Disease

- **Examples:**
 - Lupus Vasculitis
 - Rheumatoid Vasculitis
 - Sarcoid Vasculitis

Vasculitis Associated with Probable Etiology

- **Examples:**
 - Hepatitis C Virus–Associated Cryoglobulinemic Vasculitis
 - Hepatitis B Virus–Associated Vasculitis
 - Syphilis-Associated Aortitis

- Drug-Associated Immune Complex Vasculitis
- Drug-Associated ANCA-Associated Vasculitis
- Cancer-Associated Vasculitis

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Q: Takayasu's Arteritis ; Describe etiology, clinical features and management of Takayasu's arteritis

Etiology

- **Unknown Origin:** The exact etiology remains elusive.
- **Cellular Immunity:** Presence of T cells with a restricted repertoire of T-cell receptors in vascular lesions.
- **Cytokine Involvement:** Elevated expression of IL-1, IL-6, and TNF- α in active cases.
- **Genetic Predisposition:** Increased prevalence in certain ethnic populations and occasional occurrence in monozygotic twins.

Clinical Features

- **Diagnostic Challenges:** Early manifestations are often non-specific.
- **Angiographic Abnormalities:** In the aorta or its main branches.
- **Decreased Peripheral Pulses:** And/or claudication of extremities.
- **Blood Pressure Difference:** Between arms or legs of >10 mm Hg.
- **Bruits:** Over the aorta and/or its major branches.
- **Hypertension:** Defined by childhood normative data.
- **Elevated Acute-Phase Reactants:** Such as ESR or CRP.

Management

- **Corticosteroids:** First-line treatment.
- **Immunosuppressive Agents:** Methotrexate, azathioprine, and cyclophosphamide.
- **Biological Agents:** Anti-TNF agents like infliximab and adalimumab.
- **Surgical Intervention:** Vascular grafting or catheter-based angioplasty and stent placement may be necessary.

- **Aortic Valve Replacement:** May be required for significant aortic insufficiency.
- **High Recurrence:** After angioplasty and stent placement.

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Q: Henoch-Schönlein Purpura (HSP)

Henoch-Schönlein Purpura (HSP), also known as IgA vasculitis, is a small vessel vasculitis that primarily affects children.

It typically presents with palpable purpura, joint pain, abdominal pain, and kidney involvement.

Clinical Features

- **Dermatological:** Palpable purpura, predominantly in lower extremities.
- **Gastrointestinal:** Abdominal pain, often acute, diffuse, and colicky.
- **Musculoskeletal:** Arthritis or arthralgia affecting large joints like knees and ankles.
- **Renal:** Hematuria, proteinuria, and nephritic syndrome in severe cases.
- **Other:** Rarely, involvement of lungs, CNS, and scrotum.

Diagnosis

- **Classification Criteria:** Palpable purpura in the absence of coagulopathy or thrombocytopenia, along with one or more of the following: abdominal pain, arthritis or arthralgia, and IgA deposition in biopsy.
- **Laboratory Tests:** Elevated ESR, CRP, and sometimes thrombocytosis.
- **Biopsy:** Predominant IgA deposition in affected tissue.
- **Imaging:** Ultrasound for abdominal complications; renal biopsy in severe renal involvement.

Management

The management of HSP is primarily supportive, focusing on symptom relief and monitoring for complications.

Corticosteroids are used for severe manifestations, especially with significant renal or gastrointestinal involvement.

Regular follow-up is essential to monitor for renal involvement and other complications.

1. **Supportive Care:**

- **Rest and Observation:** Recommended during the acute phase, especially if joint pain is significant.
- **Pain Management:** NSAIDs (e.g., ibuprofen) for joint and abdominal pain, but with caution in renal involvement.
- **Hydration and Nutrition:** Adequate hydration and a balanced diet.

2. **Corticosteroids:**

- Indicated for severe or persistent abdominal pain, significant joint pain, or renal involvement.
- Prednisone is commonly used.
- The duration of therapy varies based on symptoms and response to treatment.

3. **Management of Renal Involvement:**

- **Mild Proteinuria and Hematuria:** Usually require only observation and regular monitoring.
- **Significant Renal Involvement:** May require corticosteroids, and in severe cases, immunosuppressive agents like cyclophosphamide or azathioprine.
- **Regular Monitoring:** Renal function and urine analysis should be monitored regularly to detect early signs of progression.

4. **Gastrointestinal Involvement:**

- Corticosteroids for severe abdominal pain or complications like intussusception.
- Monitoring for signs of bowel perforation or intussusception.

5. **Skin Care:**

- Good skin hygiene to prevent secondary infections.
- Topical treatments are not usually necessary for the purpura.

6. **Patient and Family Education:**

- Educate about the nature of the disease, its course, and symptoms to monitor.
- Reassurance about the generally good prognosis.

7. **Follow-Up:**

- Regular follow-up to monitor for recurrence or complications.
- Blood pressure and renal function monitoring are important.

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Q: Describe the diagnostic approach and management of a six-year-old child presenting with purpuric rash and pedal edema following an episode of acute diarrhoea

Diagnostic Approach

1. **Initial Assessment**

- Vital signs
- General examination to assess the extent of rash and edema

2. **History Taking**

- Onset, duration, and progression of symptoms
- Recent diarrheal episode or other infections
- Medication history
- Family history of autoimmune diseases

3. **Physical Examination**

- Skin: To assess purpuric rash
- Abdominal: For organomegaly or tenderness
- Musculoskeletal: Joint examination
- Cardiovascular: For signs of cardiac involvement

4. **Laboratory Investigations**

- Complete Blood Count (CBC)
- Urinalysis
- Serum Creatinine and Blood Urea Nitrogen (BUN)

- Coagulation profile
- C-Reactive Protein (CRP) or Erythrocyte Sedimentation Rate (ESR)
- Complement levels (C3, C4)
- Antistreptolysin O (ASO) titer or throat culture

5. *Imaging Studies*

- Ultrasound abdomen: If abdominal symptoms are present
- Chest X-ray: If respiratory symptoms are present

6. *Specialized Tests*

- Skin biopsy: If diagnosis is uncertain
- Renal biopsy: In cases of significant renal involvement

Differential Diagnosis	Key History Points	Physical Examination Clues	Diagnostic Tests
<i>Henoch-Schönlein Purpura</i>	Recent infection, abdominal pain	Palpable purpura, joint pain	CBC, Urinalysis
<i>Idiopathic Thrombocytopenic Purpura</i>	Sudden onset, may follow viral illness	Petechiae, purpura, no organomegaly	CBC, Peripheral smear
<i>Septicemia</i>	Fever, malaise	Petechiae, fever, hypotension	Blood culture, CBC
<i>Drug-Induced Vasculitis</i>	Recent medication use	Purpura, may have fever	Discontinuation of drug, CBC
<i>Systemic Lupus Erythematosus</i>	Chronic symptoms, photosensitivity	Malar rash, joint pain	ANA, dsDNA, CBC
<i>Kawasaki Disease</i>	Fever for ≥ 5 days, mucosal changes	Conjunctival injection, strawberry tongue	Echocardiogram, CBC
<i>Rheumatoid Arthritis</i>	Chronic joint pain	Joint swelling, warmth	Rheumatoid factor, CBC
<i>Leukemia</i>	Fatigue, weight loss	Pallor, petechiae, organomegaly	CBC, Bone marrow biopsy

Post-Infectious Glomerulonephritis	Recent streptococcal infection	Hypertension, edema	ASO titer, Urinalysis
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Management

1. Hospitalization

- If severe symptoms or complications are present

2. Symptomatic Treatment

- Antihistamines for itching
- Analgesics for pain

3. Corticosteroids

- Prednisolone for severe cases or renal involvement

4. Immunosuppressive Agents

- Azathioprine or Cyclophosphamide in severe or refractory cases

5. Antibiotics

- If bacterial superinfection is suspected

6. Intravenous Immunoglobulins (IVIG)

- For severe or refractory cases

7. Supportive Care

- Fluid management
- Nutritional support

8. Regular Monitoring

- Vital signs
- Laboratory parameters
- Response to treatment

9. Patient and Family Education

- Explanation of disease, treatment options, and prognosis

10. Follow-up

- Regular outpatient follow-up for monitoring and adjustment of treatment

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Q: **Criteria for diagnosis of Rheumatic fever**

- ❖ The diagnosis of Rheumatic Fever (RF) is primarily based on the Jones Criteria, which have been periodically updated to incorporate new scientific findings.
- ❖ The **modified Jones Criteria** provide a framework for the diagnosis of RF, but clinical judgment is essential, especially in atypical cases or in settings with varying prevalence of RF and access to healthcare resources.
- ❖ Early diagnosis and treatment are crucial to prevent the development of rheumatic heart disease, a serious long-term complication of RF.

Major Criteria

1. **Carditis:** Manifested by clinical findings or evidence on echocardiography. Can involve the valves (most commonly mitral and aortic).
2. **Polyarthrititis:** Migratory inflammation of large joints, typically resolving in one joint as it begins in another.
3. **Chorea:** Involuntary, rapid, irregular, and aimless movements, typically without muscle weakness.
4. **Erythema Marginatum:** A rare, non-itchy rash, primarily on the trunk and limbs.
5. **Subcutaneous Nodules:** Painless, firm collections of collagen fibers over bones or tendons. They are rare and usually occur in severe cases.

Minor Criteria

1. **Fever:** Elevated body temperature.
2. **Arthralgia:** Joint pain without swelling (considered only if polyarthrititis is not present as a major criterion).
3. **Elevated Acute Phase Reactants:** Elevated ESR (erythrocyte sedimentation rate) and/or CRP (C-reactive protein).
4. **Prolonged PR Interval:** On ECG, but only in the absence of carditis as a major criterion.

Supporting Evidence

- **Evidence of preceding Group A Streptococcal (GAS) infection:** Demonstrated by throat culture, rapid antigen detection test, or elevated or rising streptococcal antibody titer.

Diagnostic Application

- **Initial Episode of RF:** Requires the presence of either two major criteria, one major and two minor criteria, or evidence of preceding GAS infection plus two minor criteria.
- **Recurrent Episode of RF:** In patients with a history of RF or rheumatic heart disease, the presence of two minor criteria or one major plus one minor criterion may suffice, especially if there is evidence of a recent GAS infection.

Special Considerations

- **Chorea:** May occur as a late manifestation and can be the sole presentation of RF. In such cases, other criteria may not be present.
- **Low-Risk Populations:** In populations with low incidence of RF, stricter application of the criteria is recommended to avoid over-diagnosis.

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Q: Prophylaxis of Rheumatic fever

- ❖ Prophylaxis of Rheumatic Fever (RF) is crucial in preventing recurrent attacks and the development of rheumatic heart disease (RHD)
- ❖ The prophylaxis strategy primarily focuses on preventing Group A Streptococcal (GAS) infections and managing them promptly when they occur
- ❖ The goal of RF prophylaxis is to prevent the progression to RHD, a major cause of morbidity and mortality in many parts of the world
- ❖ The success of prophylaxis depends on strict adherence to the antibiotic regimen and regular medical follow-up.

Primary Prophylaxis

- **Objective:** To treat the initial streptococcal pharyngitis, thereby preventing the first episode of RF.
- **Antibiotics:** Penicillin (either a single injection of benzathine penicillin G or a course of oral penicillin) is the first choice. For those allergic to penicillin, erythromycin or other suitable antibiotics can be used.
- **Identification and Treatment:** Rapid identification and treatment of streptococcal pharyngitis in children and adolescents are essential.

Secondary Prophylaxis

- **Objective:** To prevent recurrent attacks of RF, particularly in individuals with a history of RF or RHD.
- **Long-Term Antibiotic Prophylaxis:**
 - **Benzathine penicillin G:** Intramuscular injections every 3-4 weeks are the preferred method.
 - **Oral Penicillin:** An alternative for those who cannot receive injections, but less effective due to compliance issues.
 - **Erythromycin or other macrolides:** For patients allergic to penicillin.
- **Duration of Prophylaxis:**
 - **Without Carditis:** At least 5 years or until age 21, whichever is longer.
 - **With Carditis but no Residual Heart Disease:** At least 10 years or well into adulthood, whichever is longer.
 - **With Carditis and Chronic RHD:** At least 10 years or until at least age 40, with some recommending lifelong prophylaxis.

Monitoring and Compliance

- **Regular Follow-Up:** To ensure adherence to prophylaxis and monitor for side effects.
- **Education:** Patients and families should be educated about the importance of adherence to prophylaxis.

Special Considerations

- **Pregnancy:** Women with a history of RF/RHD should continue prophylaxis during pregnancy and delivery.
- **Dental Procedures:** Antibiotic prophylaxis before dental procedures is not routinely recommended for patients with a history of RF without valve disease.

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Q: Macrophage activation syndrome

- ❖ Macrophage Activation Syndrome (MAS) is a severe, potentially life-threatening complication of rheumatic diseases, most commonly seen in systemic juvenile idiopathic arthritis (sJIA) and systemic lupus erythematosus (SLE).

- ❖ It is a form of secondary hemophagocytic lymphohistiocytosis (HLH) and is characterized by excessive activation and proliferation of macrophages and T lymphocytes, leading to a cytokine storm and multi-organ dysfunction.

Pathophysiology

- **Immune Dysregulation:** Triggered by an aberrant immune response, leading to uncontrolled activation of macrophages and T cells.
- **Cytokine Storm:** Overproduction of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, interferon-gamma, and tumor necrosis factor-alpha.
- **Hemophagocytosis:** Activated macrophages phagocytose blood cells, leading to cytopenias.

Clinical Features

- **Fever:** Often high and persistent.
- **Hepatosplenomegaly:** Enlargement of liver and spleen.
- **Cytopenias:** Affecting one or more cell lines (anemia, leukopenia, thrombocytopenia).
- **Liver Dysfunction:** Elevated liver enzymes, jaundice.
- **Coagulopathy:** Manifesting as prolonged clotting times, increased D-dimer.
- **Neurological Manifestations:** Irritability, disorientation, seizures, coma.
- **Rash:** Non-specific skin rash may be present.

Diagnosis

- **Laboratory Findings:** Elevated ferritin (often markedly high), elevated liver enzymes, low ESR (despite active inflammation), hypertriglyceridemia, hypofibrinogenemia.
- **Bone Marrow Aspiration:** May show hemophagocytosis but is not always necessary for diagnosis.
- **HLH-2004 Diagnostic Criteria:** Often used, although not specifically designed for MAS.

HLH-2004 Diagnostic Criteria

These criteria are often used as a reference for diagnosing MAS, although they were originally developed for primary HLH:

1. **Fever:** Persistent fever of unknown origin.
2. **Splenomegaly:** Enlargement of the spleen.
3. **Cytopenias:** Affecting at least two of three lineages in the peripheral blood:
 - Hemoglobin <9 g/dL (in infants <4 weeks: <10 g/dL)
 - Platelets <100,000/ μ L
 - Neutrophils <1,000/ μ L
4. **Hypertriglyceridemia and/or Hypofibrinogenemia:**
 - Fasting triglycerides $\geq$ 265 mg/dL
 - Fibrinogen $\leq$ 150 mg/dL
5. **Hemophagocytosis:** In bone marrow, spleen, or lymph nodes without evidence of malignancy.
6. **Low or Absent Natural Killer (NK) Cell Activity:** Typically measured in a specialized laboratory.
7. **Ferritin:** High levels of ferritin, often >500 ng/mL, but in MAS, levels can be much higher.
8. **Soluble CD25 (sIL-2R):** Elevated levels, indicating T-cell activation and proliferation.

Additional Considerations for MAS

- **Ferritin:** Extremely high levels (often >10,000 ng/mL) are more suggestive of MAS, especially in the context of a rheumatic disease.
- **Liver Enzyme Elevation:** Often more pronounced in MAS compared to primary HLH.
- **Coagulation Abnormalities:** Including prolonged clotting times, which may be more common in MAS.
- **Rapid Drop in Erythrocyte Sedimentation Rate (ESR):** Paradoxically, ESR may drop due to fibrinogen consumption, despite active inflammation.

Rheumatology-Specific Criteria for MAS

In the context of sJIA and other rheumatic diseases, additional criteria have been proposed to aid in the diagnosis of MAS:

1. **Rapidly Rising Ferritin Levels:** Doubling of ferritin within a short period.
2. **Decreased Platelet Count:** Rapid drop over a few days.
3. **Elevated Liver Enzymes:** Particularly aspartate aminotransferase (AST).
4. **Central Nervous System Dysfunction:** Including irritability, disorientation, or seizures.
5. **Coagulopathy:** Distinguished by low fibrinogen and elevated D-dimer levels.

Management

- **High-Dose Corticosteroids:** First-line treatment.
- **Cytokine Inhibition:** IL-1 and IL-6 inhibitors (e.g., Anakinra, Tocilizumab) have been effective, especially in sJIA-associated MAS.
- **Cyclosporine A:** An immunosuppressant that can be effective.
- **Intravenous Immunoglobulin (IVIG):** May be used in refractory cases.
- **Etoposide and Hematopoietic Stem Cell Transplantation (HSCT):** Considered in severe, refractory cases or in primary HLH.

Prognosis

- **Variable Outcome:** Can range from full recovery to fatal outcome, depending on severity and response to treatment.
- **Importance of Early Recognition and Treatment:** Prompt intervention can significantly improve outcomes.

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Q: Tabulate the differences in clinical and laboratory features of Kawasaki disease and MIS-C.

- ❖ **Kawasaki Disease** is primarily a disease of young children and is characterized by specific clinical criteria, with coronary artery involvement being a significant concern.
- ❖ **MIS-C** is a condition associated with COVID-19, presenting with more systemic involvement, including significant gastrointestinal and cardiovascular symptoms, and more severe laboratory abnormalities.
- ❖ Treatment for both conditions includes immunomodulatory therapies, but the approach can vary based on the severity and specific manifestations of the disease.

Feature	Kawasaki Disease (KD)	Multisystem Inflammatory Syndrome in Children (MIS-C)
<i>Etiology</i>	Unknown, but thought to be related to infectious triggers.	Associated with COVID-19, often following SARS-CoV-2 infection.
<i>Age Group</i>	Typically affects children under 5 years of age.	Affects a broader age range, including older children and adolescents.
<i>Clinical Presentation</i>	Persistent fever. Conjunctival injection. Rash. Cervical lymphadenopathy. Changes in lips and oral cavity. Extremity changes (swelling, erythema).	Persistent fever. Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). Cardiovascular involvement (shock, myocarditis). Mucocutaneous symptoms (can overlap with KD). Neurological symptoms in some cases.
<i>Cardiac Involvement</i>	Coronary artery aneurysms are a hallmark.	More diverse, including myocarditis, pericarditis, and coronary artery dilation or aneurysms.
<i>Laboratory Findings</i>	Elevated inflammatory markers (ESR, CRP). Normocytic anemia. Thrombocytosis (after the first week). Sterile pyuria.	Markedly elevated inflammatory markers (ESR, CRP, ferritin). Lymphopenia. Thrombocytopenia. Elevated cardiac markers (troponin, BNP). Coagulopathy indicators (elevated D-dimer, prolonged PT/PTT).
<i>Treatment</i>	Intravenous immunoglobulin (IVIG). Aspirin.	IVIG. Corticosteroids. Aspirin. Additional immunomodulatory therapies in severe cases (e.g., tocilizumab).
<i>Association with COVID-19</i>	No direct association.	Directly associated with recent or current SARS-CoV-2 infection.
<i>Epidemiology</i>	Consistent incidence unrelated to COVID-19 pandemic.	Emerged in the context of the COVID-19 pandemic, with cases peaking after COVID-19 waves.

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